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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,757	09/01/2006	Nobuhiko Fushimi	Q96646	6348

23373 7590 06/20/2007
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EXAMINER

RAHMANI, NILOOFAR

ART UNIT	PAPER NUMBER
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1625

MAIL DATE	DELIVERY MODE
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06/20/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/591,757

Applicant(s)

FUSHIMI ET AL.

Examiner

Niloofar Rahmani

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 and 27-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-22 and 27-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-22, 27-31 are currently pending in the instant application and claims 23-26, and 32-34 are cancelled.

Priority

2. This application is filed on 09/01/2006, which is a 371 of PCT/JP05/04145, filed on 03/03/2005, which claims priority of JAPAN 2004-61426, filed on 03/04/2004.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22, 27-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-22, 27-31 are rejected because the term "substituent group □" is confusing. On line 9 of the claim 1, the term "substituent group □" is vague and ambiguous because there is no definition for this term in the claim. Correction is required.

4. Claims 11-16, 18, and 28 are rejected because the term "A human SGLT inhibitor" is vague and ambiguous. Does the applicant mean a compound claims or pharmaceutical composition claims or method for treating using the compounds in claim 1.

5. Claims 10, 17, and 27 are rejected because the claims are self-conflicting. Pharmaceutical composition by definition must be effective yet non-toxic. Claims

10,17, and 27 are cosmetic composition without dosage limitation i.e. included both ineffective and toxic amount. It is recommended that "therapeutically effective amount" be incorporated in the claims.

6. Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22, 27-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active

compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is not found in the specification.

c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al,

Art Unit: 1625

"Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1.

7. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-22, 27-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification lacks enablement

Art Unit: 1625

of the term "disease associated with hyperglycemia", which are claimed in the method claims. While enabling for "plasma glucose concentration for diabetic rat model", which are on page 187-188 of the instant specification, it is not seen where this enables other types of "disease associated with hyperglycemia".

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims.
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to a method for treating a disease associated with hyperglycemia, which comprises administering

Art Unit: 1625

an effective amount of a nitrogen-containing fuse-ring derivative as claimed in claim 1.

The state of the prior art: " Both ANP and ET-3, which are potent diuretic and natriuretic substances, dramatically reduce SGL2 activity. SGL2 is the low-affinity, high-capacity SGLT responsible to reabsorb the bulk of filtered glucose and sodium in the renal proximal convoluted tubule. Taking together, the data strongly support the idea that SGLT2 inhibition is part of ANP and ET-3 diuretic- and natriuretic-action mechanism. The results suggest that ANP- and ET-3-induced SGLT2 inhibition has occurred through a direct modification of the protein. The findings indicate that the renal SGLT could be a new potential candidate for drug target in the treatment of patients with pathologies involving hydro-saline balance deregulation, such as Diabetes Mellitus and certain types of hypertension." (Majowicz et al., Peptides, 2003, Vol. 24, pages 1971-1976).

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

Amount of guidance/working examples: On pages 182-186 of the specification, applicant has examples of test compounds for inhibition of human SGLT1, SGLT2 activity and on pages 187-188 of the specification, applicant has examples of test compounds and inhibitory effects on blood glucose level. However, applicant has no guidance or examples of test compounds and other types of "disease associated with hyperglycemia".

The breadth of the claims: The breadth of claims is drawn to a method for treating a disease associated with hyperglycemia, which comprises administering an effective amount of a nitrogen-containing fuse-ring derivative as claimed in claim 1.

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating tumor disease, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 19-22, 27-31, for treating a disease associated with hyperglycemia, which

Art Unit: 1625

comprises administering an effective amount of a nitrogen-containing fuse-ring derivative as claimed in claim 1, have been enabled by the instant specification.

8. Claims 19-22, 27-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before occurs.

This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 24-27, page 16 to line 3, page 17 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to medical treatment and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted with diseases before the fact. 6) The artisan using Applicants invention would be a Board Certified physician who specialized to treat diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of disease associated with hyperglycemia generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent disease associated with hyperglycemia generally. That is, the skill is so low that no compound effective generally against disease associated with hyperglycemia has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of

Art Unit: 1625

unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula (I).

The Examiner suggests deletion of the word "prevention".

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas Mckenzie, can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI

06/08/2007

NL



D. MARGARET SEAMAN

PRIMARY EXAMINER

ART UNIT 1625